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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/642,409 | 08/15/2003 | Deborah Ann Ansaldi | P1363R1C1 | 1482 |

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Attn: Janet E. Hasak
Genentech, Inc.
1DNA Way
South San Francisco, CA 94080

| EXAMINER | |
|---|---|
| HOLLERAN, ANNE L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1643 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 03/01/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/642,409 | ANSALDI ET AL. | |
| | Examiner | Art Unit | |
| | Anne L. Holleran | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1, 5-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 5-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. The amendment filed 11/27/2006 is acknowledged. Claims 2-4, 14 and 15 were canceled. Claims 1 and 5 –15 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Claim Rejections Withdrawn:***

### *Claim Rejections - 35 USC § 102*

3. The rejection of claims 1, 6, 8-10, 14 and 15 under 35 U.S.C. 102(b) as being anticipated by Wan (US 6,177,548; published Jan. 23, 2001; effective filing date 10/14/1997) as evidenced by Li (Li, F. et al, www.bioprocessingjournal.com, September/October, 2005, pages 1-8 in vol. 4(5): page 23) is withdrawn in view of the amendment to claim 1 and the cancellation of claims 14 and 15.

4. The rejection of claims 1, 5, 6, 8-12, 14 and 15 under 35 U.S.C. 102(b) as being anticipated by Jiskoot (Jiskoot, W. et al., Develop. Biol. Standard., Vol. 71: 73-78, 1990) as evidenced by Li (supra) is withdrawn in view of the amendment to claim 1 and the cancellation of claims 14 and 15.

5. The rejection of claims 1, 5, 7, and 11 under 35 U.S.C. 102(b) as being anticipated by Bodo (U.S. 5,196,323; published Mar. 23, 1993) is withdrawn in view of the amendment to claim 1.

6. The rejection of claims 1, 2, 4, 6, 7 and 9 under 35 U.S.C. 103(a) as being unpatentable over Gooding (Gooding, K.M. and Schmuck, M.N. Journal of Chromatography, 327: 139-146, 1985) in view of Gagnon (Gagnon, P. et al, Purification Tools for Monoclonal Antibodies, pages 67-86, Validated Biosystems, Inc., Tucson, AZ, 1996; cited in the IDS) is withdrawn in view of amendment to claim 1 and the cancellation of claims 2 and 4.

***Double Patenting***

7. The rejection of claims 1-15 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,620,918 is withdrawn in view of the terminal disclaimer filed 11/27/2006.

***New Grounds of Rejection:***

***Claim Rejections - 35 USC § 112***

8. Claims 1 and 5-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because step (b) contains the recitation "wherein the monomer yield is greater than 90%", which implies step (b) includes a recovery step. However, claim 1 contains the recitation of step (c), directed to recovering the monomer. Therefore, it is not clear what the phrase "the monomer yield is greater than 90%" means, because yield cannot be determined until after the monomer is recovered. Alternatively, claim 1 is indefinite because it is not clear what is intended by the step (c), the recovery step, since a yield is determined in step (b).

***Claim Rejections - 35 USC § 103***

9. Claims 1, 6, 7, 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaudhary (Chaudhary, V.K. et al., Nature, 339, pages 394-397; cited in IDS) in view of Graf (Graf, H. et al, Bioseparation, 4: 7-20, 1994; cited in IDS) together with Gemski (Gemski, M.J. et al. BioTechniques, 3(5): 378-284, 1985; cited in IDS), Hakalahti (Hakalahti, L. et al. Journal of Immunological Methods, 117: 131-136, 1989), and further in view of Ghettie (Ghettie, M.-A., et al. Proc. Natl. Acad. Sci. USA, 94: 7509-7514, 1997).

Claim 1 has been amended to read on a method for purifying polypeptide monomers from a mixture consisting essentially of said polypeptide monomers, and dimers or multimers of said polypeptide monomers or both dimer and multimers of said polypeptide monomers of said polypeptide monomers, wherein the polypeptide is anti-IgE, anti-IgG, anti-Her2, anti-CD11a, anti-CD18, anti-CD20 anti-VEGF, or IgE. The method comprises the active steps of applying the mixture to a cation-exchange or anion-exchange chromatography resin, eluting the mixture at a gradient of about 0-1 M of an elution salt, wherein the monomer is purified from the dimers or multimers or both present in the mixture, and wherein the monomer yield is greater than 90%,

and recovering the monomer. As discussed in the previous Office action, the mixture applied to the ion exchange resin is construed as "comprising" polypeptide monomers, and dimers or multimers or both dimers and multimers, because the present specification defines the "mixture" as "containing" (which has the same meaning as "comprising") monomers and either dimers or multimers or both (page 5, lines 23-24). Therefore, the transitional phrase "consisting essentially of" appears to have the same meaning as comprising (see MPEP 2111.03, where "consisting essentially of" limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed inventions. For the purposes of searching for and applying prior art, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising").

Chaudhary teaches a method of purifying the monomeric form of an anti-Tac(fv)-PE40 fusion protein from higher molecular weight aggregates (see page 395, column 1 and Figure 2). The mixture applied to the column in Chaudhary is 100,000g pellet from sonicated spheroplasts. Chaudhary teaches that fractions 32-33 from an anion exchange column eluate (see lane 4) appears to be free of higher molecular weight dimers or multimers. The elution salt was NaCl, and the gradient was 0 – 500 mM.

While Chaudhary teaches applying a mixture that comprises antibody monomers and dimers and higher molecular weight multimers, Chaudhary is silent on the yield of monomer and does not teach this method using mixtures comprising polypeptides that are anti-IgE, anti-IgG, anti-Her2, anti-CD11a, anti-CD18, anti-CD20 anti-VEGF, or IgE.

However, the use of ion-exchange chromatography to purify mixtures containing antibodies is known in the prior art, and the prior art methods have recovered 90% of the antibody. For example, Graf teaches purification of monoclonal antibodies using ion-exchange chromatography where the recovery of the Mab is greater than 90% with purity ranging from 70% to 95% (see Table 1, page 11). Gemski teaches use of anion exchange chromatography with recoveries of 95% (see Table 2, page 381). Hakalahti teaches cation exchange chromatography followed by anion exchange chromatography with recovery over 90% and purity of 95% (see page 136, 1st colymn). Hakalahti also teaches that recovery by gel filtration is only 60% (see page 136).

None of Graf, Gemski, or Hakalahti teaches methods where the mixture applied to the column is a mixture of polypeptide monomers and dimers or multimers or monomers and both dimers and multimers, where the polypeptide is anti-IgE, anti-IgG, anti-Her2, anti-CD11a, anti-CD18, anti-CD20 anti-VEGF, or IgE.

However, Ghettie teaches making dimers from anti-Her2 antibodies and anti-CD20 antibody as well as other antibodies, and teaches separating the monomer from the dimer form, and recovering both the monomer and the dimer for the purpose of comparing the effect of the monomeric form to the effect of the dimeric form on the ability of the antibodies to induce growth arrest or apoptosis of tumor cells. Ghettie separates the monomer from the dimer using size exclusion chromatography (gel filtration).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the Chaudhary ion exchange chromatography method instead of size exclusion chromotagraphy for the separation of dimeric from monomeric forms of

either Ghettie's anti-Her2 antibody or anti-CD20 antibody, because the techniques were well known in the prior art for making methods comprising ion exchange chromatography for the purpose of recovering pure preparations of antibodies, as evidenced by the teachings of Chaudhary, Graf, Gemski, or Hakalahti. One would have been motivated to use ion exchange chromatography over gel filtration because Hakalahti teaches that gel filtration produces a lower yield of pure antibody product when compared to ion exchange chromatography.

10. Claims 1, 5, 7, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lynch (Lynch, P., Genetic Engineering News, page 17, November 1, 1997; cited in the IDS) in view of Graf (Graf, H. et al, Bioseparation, 4: 7-20, 1994; cited in IDS) together with Gemski (Gemski, M.J. et al. BioTechniques, 3(5): 378-284, 1985; cited in IDS), Hakalahti (Hakalahti, L. et al. Journal of Immunological Methods, 117: 131-136, 1989), and further in view of Ghettie (Ghettie, M.-A., et al. Proc. Natl. Acad. Sci. USA, 94: 7509-7514, 1997).

Lynch teaches that a protein A purified cell culture medium was applied to a cation exchange column and eluted by a linear salt gradient, separating the monomer from the aggregated forms of the antibody. Lynch is silent on the yield of monomer and does not teach this method using mixtures comprising polypeptides that are anti-IgE, anti-IgG, anti-Her2, anti-CD11a, anti-CD18, anti-CD20 anti-VEGF, or IgE.

However, the use of ion-exchange chromatography to purify mixtures containing antibodies is known in the prior art, and the prior art methods have recovered 90% of the antibody. For example, Graf teaches purification of monoclonal antibodies using ion-exchange chromatography where the recovery of the Mab is greater than 90% with purity ranging from

70% to 95% (see Table 1, page 11). Gemski teaches use of anion exchange chromatography with recoveries of 95% (see Table 2, page 381). Hakalahti teaches cation exchange chromatography followed by anion exchange chromatography with recovery over 90% and purity of 95% (see page 136, 1st colymn). Hakalahti also teaches that recovery by gel filtration is only 60% (see page 136).

None of Graf, Gemski, or Hakalahti teaches methods where the mixture applied to the column is a mixture of polypeptide monomers and dimers or multimers or monomers and both dimers and multimers, where the polypeptide is anti-IgE, anti-IgG, anti-Her2, anti-CD11a, anti-CD18, anti-CD20 anti-VEGF, or IgE.

However, Ghettie teaches making dimers from anti-Her2 antibodies and anti-CD20 antibody as well as other antibodies, and teaches separating the monomer from the dimer form, and recovering both the monomer and the dimer for the purpose of comparing the effect of the monomeric form to the effect of the dimeric form on the ability of the antibodies to induce growth arrest or apoptosis of tumor cells. Ghettie separates the monomer from the dimer using size exclusion chromatography (gel filtration).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the Lynch ion exchange chromatography method instead of size exclusion chromotagraphy for the separation of dimeric from monomeric forms of either Ghettie's anti-Her2 antibody or anti-CD20 antibody, because the techniques were well known in the prior art for making methods comprising ion exchange chromatography for the purpose of recovering pure preparations of antibodies, as evidenced by the teachings of Lynch, Graf, Gemski, or Hakalahti. One would have been motivated to use ion exchange

chromatography over gel filtration because Hakalahti teaches that gel filtration produces a lower yield of pure antibody product when compared to ion exchange chromatography.

11. Claims 1, 5, 8-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jiskoot (Jiskoot, W. et al., Develop. Biol. Standard., Vol. 71: 73-78, 1990; of record) as evidenced by Li (of record) in view of Ghettie (Ghettie, M.-A., et al. Proc. Natl. Acad. Sci. USA, 94: 7509-7514, 1997; cited in IDS) and further in view of Hakalahti (supra).

Jiskoot teaches a method for purifying the MN12 monoclonal antibody using cation-exchange from bovine IgG present in fetal bovine serum with a yield of 91% (see Table III, page 77). The method also appears to result in the purification of antibody monomer from antibody multimers (see Table III, page 77 "Gel Permeation pattern (%monomers)"). The pH with cation exchange chromatography is 6.5. The mixture applied to the ion exchange columns is a protein A column eluate that was buffer exchanged. Li teaches that protein A chromatography does not remover dimers and aggregates, see page 5). Thus, Jiskoot's mixture appears to be a mixture of antibody monomers and dimers or multimers. The gradient appears to be stepwise (a wash buffer, followed by an elution buffer (see Table II)). The elution salt is 0.08M NaCl.

Jiskoot does not teach a method where the mixture applied to the column is a mixture of polypeptide monomers and dimers or multimers or monomers and both dimers and multimers, where the polypeptide is anti-IgE, anti-IgG, anti-Her2, anti-CD11a, anti-CD18, anti-CD20 anti-VEGF, or IgE. Hakalahti teaches that recovery of purified antibody by gel filtration is only 60% (see page 136) compared with a recovery of greater than 90% using an ion-exchange chromatography method. Niether Jiskoot nor Hakalahti teaches methods where the mixture

applied to the column is a mixture of polypeptide monomers and dimers or multimers or monomers and both dimers and multimers, where the polypeptide is anti-IgE, anti-IgG, anti-Her2, anti-CD11a, anti-CD18, anti-CD20 anti-VEGF, or IgE.

However, Ghettie teaches making dimers from anti-Her2 antibodies and anti-CD20 antibody as well as other antibodies, and teaches separating the monomer from the dimer form, and recovering both the monomer and the dimer for the purpose of comparing the effect of the monomeric form to the effect of the dimeric form on the ability of the antibodies to induce growth arrest or apoptosis of tumor cells. Ghettie separates the monomer from the dimer using size exclusion chromatography (gel filtration).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the Jiskoot ion exchange chromatography method instead of size exclusion chromatography for the separation of the dimeric from the monomeric form of either Ghettie's anti-Her2 antibody or anti-CD20 antibody, because the techniques were well known in the prior art for making methods comprising ion exchange chromatography for the purpose of recovering pure preparations of antibodies, as evidenced by the teachings of Jiskoot. One would have been motivated to use ion exchange chromatography over gel filtration because Hakalahti teaches that gel filtration produces a lower yield of pure antibody product when compared to ion exchange chromatography.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
February 26, 2007

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER